ZSTK - FOXO1A HYSTERESIS

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1. A possible explaining mechanism

In physics, hysteresis describes systems that do not directly follow the forces applied to them, but react slowly, or do not return completely to their original state. This phenomenon is common in magnetism, specifically in ferromagnetic materials. For mechanical engineers hysteresis is a common phenomenon appearing for instance in friction models (see [2]). As far as dynamic enzyme models are concerned, hysteresis has been studied from the beginning of research of enzymatic reactions from a mathematical point of view (see for instance the early work [1], which discusses hysteresis in a reversible enzymatical reaction based on Henri's original stoichiometric equation). Before going to the discussion of the case that concerns this work, let us to briefly expose some ideas concerning hysteresis in controlled system.

Figure 1 shows the two basic kinds of hysteresis: clockwise CW hysteresis (Figure 1-(a)) and counter clockwise (CCW) hysteresis (Figure 1-(b)). In the first case signal Y precedes signal X (Figure 1-(c)), while signal Y lags signal X in the second case (Figure 1-(d)). The oscillatory behaviors shown in Figure 1 correspond to repetitive hysteresis loops. When considering controlled-systems, it has been established that hysteresis appears as related to dominant feedback regulation responding to oscillatory perturbations: CC hysteresis for dominant negative feedback at high frequency perturbations and CCW hysteresis for dominant positive feedback at low frequency perturbations, for controlled system regulated by the two kinds of feedback (purely CC hysteresis only appear when negative feedback is the only regulating mechanism, while purely CCW hysteresis only appear when positive feedback is the only regulating mechanism; in both cases for any disturbance's frequency). In biomolecular controlled systems this hysteresis phenomenon (related to a two feedback loops regulating scheme) has been observed in the force-lenght relation in sarcomeres affected by oscillatory disturbances affecting the length of this fundamental component of muscle filaments, see [3] and the references therein for the details.

As far as the hysteretical experimentally observed behavior is concerned, Figure 2 shows the experimental results. As can be seen in Figure 2-(a), the Zstk - FOXO1a shows CW hysteresis, which strongly suggests that an underlying dominant negative feedback regulator is working when only Pi3K is inhibited (the crossover behavior of the hysteresis loop observed in Figure 2-(a) suggest dominancy vanishing of the involved negative feedback regulator). When Pi3K and mTOR are inhibited simultaneously the Zstk - FOXO1a shows mixed CW hysteresis and CCW hysteresis, which suggest two possible aternatives: dominancy variations between negative and positive regulation or *no feedback mechanism*

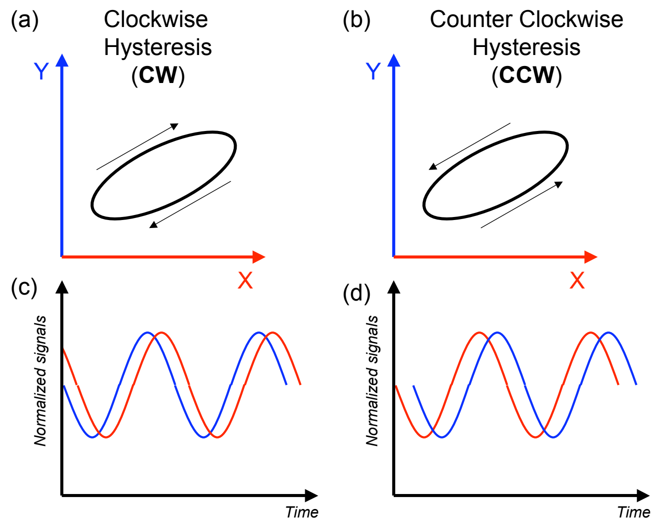

FIGURE 1. This figure shows both clockwise hysteresis and counter clockwise hysteresis behaviors. Signal X is shown in red and signal Y is shown in blue. (a) and (b) correspond to the X-Y planes for clockwise hysteresis and counter clockwise hysteresis, respectively. The time evolution of X and Y is shown in (c) for CW hysteresis and in (d) for CCW hysteresis, respectively. The frequency of the signals corresponds to the reciprocal of the time required for a hysteresis loop in the corresponding X-Y plane. Note that Y precedes X in the CW hysteresis case, while Y lags X in the CCW hysteresis case.

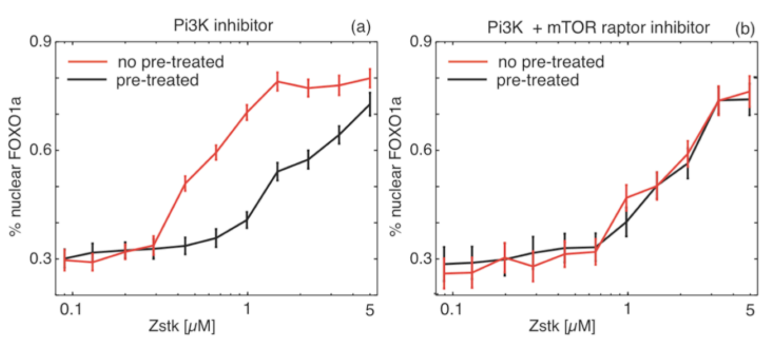

FIGURE 2. Experimentally observed hysteresis. (a)

working. If the suggested regulatory mechanism uncovered by the application of the Zstk give rise to the observed observed hysteresis phenomena, a purely positive actions would be shown by the system when opening the negative feedback loop.

References

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[3] Y. Yaniv, R. Sivan, and A. Landersberg (2005): Analysis of hysteresis in force length and force calcium relations. *Am J Physiol Heart Circ Physiol*, 288: H389-H399.